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10/561,618	05/05/2006	Brenda F. Baker	CORE0005USA	9771

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WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
07/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,618	BAKER, BRENDA F.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,38,40 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,38,40 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Double Patenting

Claims 1, 38 and 40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 9, 11, 79 and 80 of copending Application No. 10/700,689 in view of Brown et al. (US 2003/0166282).

The instant claims are directed to compositions of oligomeric compounds comprising a sense and antisense strand wherein the antisense strand comprises at least one 2'-fluoro nucleoside and the sense strand comprises an inosine base at the 3' terminus and a C or G at the 5' terminus. In specific embodiments the compounds are 12-30 or 19-23 nucleotides in length.

The claims of the '689 application are directed to compositions of sense and antisense strands wherein at least one strand is a chimeric oligomeric compound having at least two 2'-F modified nucleosides. The claims of the '689 application differ from the instant claims in that they do not explicitly recite the presence of one or more inosine nucleobases in the sense strand, including at the 3' terminus. However, the '689 specification contemplates at paragraph 138 the inclusion of modified nucleobases including hypoxanthine, another name for inosine.

Brown et al. teach that the inclusion of nucleotide analogs reduces duplex stability of a siRNA and increases its potency. Brown et al. teach that inosine is one base that will provide this effect and that this nucleoside can be easily incorporated into a nucleic acid using the appropriate phosphoramidite. Therefore, based on the teaching of the '689 application that inosine can be included in a chimeric oligomeric compound and the teachings of Brown that inosine in a siRNA will increase siRNA potency by decreasing duplex stability and the recognition that placement of inosine at a particular position within an oligonucleotide is a matter of design choice, the instant claims are an obvious variation of the claims of the '689 application.

This is a provisional obviousness-type double patenting rejection.

Response to Arguments: Double Patenting

Applicants' willingness to file a terminal disclaimer upon identification of allowable subject matter is acknowledged, however it is proper to maintain the provisional double patenting rejection until that time.

Claim Rejections - 35 USC § 103

Claims 1, 38, 40 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fosnaugh et al. in view of Brown et al. (both of record).

The claims are directed to compositions of oligomeric compounds comprising a sense and antisense strand wherein the antisense strand comprises at least one 2'-fluoro nucleoside and the sense strand comprises an inosine base at the 3' terminus and a C or G at the 5' terminus. In specific embodiments the compounds are 12-30 or

19-23 nucleotides in length or the antisense comprises 2'-fluoro at each nucleotide position.

Fosnaugh et al. teach siRNAs that are about 19 to about 25 nucleotides in length and comprise an antisense region complementary to a sequence encoding a target RNA and a sense region complementary to the antisense region. At paragraph 34 Fosnaugh et al. teach the use of chemically modified siRNAs, with chemical modifications including 2'-deoxy-2'-fluoro ribonucleotides, which improve the stability of the interaction with the target RNA sequence and to improve nuclease resistance. Fosnaugh et al. additionally teach that "universal bases" may be included in a siRNA, teaching at paragraph 129 that inosine is an example of a universal base. At paragraph 50 Fosnaugh et al. teach that 2'-deoxy-2'-fluoro modified nucleotides and universal base modifications can be present in either the sense strand, the antisense strand or both strands and in Table III specifically teach 21 nucleotide siRNAs wherein the antisense strand comprises 2'-fluoro nucleosides and a G at the 5' terminus. Fosnaugh et al. teach modifications to nucleotides in a permissive manner, describing at paragraph 43 for example that a siRNA can comprise any naturally or non-naturally occurring nucleobase and also describing at paragraph 50 that a siRNA can comprise "5 or more" 2'-fluoro nucleotides, but Fosnaugh et al. does not explicitly teach a siRNA wherein every position contains a 2'-fluoro modified nucleotide, nor does this reference explicitly teach the inclusion of inosine at the 3' terminus of the sense strand.

Brown et al. teach siRNAs comprising modified nucleotides that have the effect of decreasing the duplex stability of the dsRNA. Brown et al. teach at paragraph 29 that such siRNAs are significantly more potent. At paragraph 33 Brown et al. teach that

because I:C base pairs form only two hydrogen bonds instead of the three in G:C base-pairs, substitution of inosine (I) for G at one or more positions in the siRNA will reduce duplex stability and thereby enhance siRNA potency. At paragraph 196 Brown et al. teach that inosine can be substituted for guanosine in any siRNA sequence by using an appropriate inosine phosphoramidite.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make siRNAs comprising 2'-fluoro modified nucleosides as taught by Fosnaugh et al. with one or more inosine bases that will reduce duplex stability as taught by Brown et al. Brown et al. provide a motivation to include inosine nucleotides in a siRNA by teaching that use of such an analog will reduce duplex stability and increase potency of the siRNA and provides a reasonable expectation of success in making siRNAs comprising inosine by teaching that inosine can be easily substituted for guanosine using an appropriate phosphoramidite. Based on the permissive manner in which Fosnaugh et al. teach the inclusion of 2'-fluoro modified nucleotides and the knowledge that such nucleotides can be incorporated into an oligomer using commercially available reagents and routine synthetic methods, one of ordinary skill in the art would recognize the production of a siRNA comprising 2'-fluoro nucleotides at every position of the antisense strand to be a matter of design choice that would be made in the course of routine optimization. Based on the suggestion by Brown et al. of including inosine nucleotides in a siRNA and their teaching that such nucleosides are easily substituted for guanosine using routine synthetic methods and readily available reagents, one of ordinary skill in the art would recognize that placement of the inosine at any particular position, including the 3' terminus of the sense

strand, is a matter of design choice that would be made in the course of routine optimization.

Thus, the invention of claims 1, 38, 40 and 58 would have been obvious, as a whole, at the time the invention was made.

Response to Arguments

Applicants traverse the rejection over Fosnaugh et al. in view of Brown et al. by arguing the Fosnaugh et al. do not teach or suggest oligomeric compounds bearing the particular pattern of chemical modifications claimed, but provide only generalized teachings regarding chemical modification of RNA that could be incorporated into oligomeric compounds in a large number of possible patterns and combinations. Applicants further argue the oligonucleotides described in Fosnaugh et al. possess the same modification for each type of nucleobase throughout the oligonucleotide and that this indicates Fosnaugh et al. teach patterns of modifications that depend on base sequence. Applicants conclude that Fosnaugh et al. teach away from the core concept of sequence-independent patterns of modification while the instant claims identify particular positions or patterns of modification independent of the base sequence of the oligomer.

These arguments are not persuasive because Fosnaugh does not teach away from the sequence-independent patterns of modification. While Fosnaugh et al. do teach that in one embodiment the 2'-fluoro modifications are at pyrimidine nucleobases, this does not teach away from sequence independent modification because Fosnaugh et al. also explicitly contemplate an siRNA wherein the antisense strand comprises one

or more 2'-fluoro modified sugars, the same limitation recited in instant claim 1 (see paragraph 52). Fosnaugh et al. also teach the presence of 2'-fluoro sugars in the antisense strand, teaching that this strand can have 5 or more such modifications, which one of ordinary skill would recognize could extend to each position of the antisense strand.

Applicants argue that Brown et al. indicate a variety of techniques to reduce the stability of the siRNA duplexes, including introducing nucleotide analogs, but do not suggest that incorporation of an inosine base would be any more advantageous or desirable than incorporation of any of the other chemical modifications described in the application.

Applicants further argue that Brown et al. do not describe introducing at least one 2'-fluoro modified nucleoside into the antisense strand of the siRNA molecules and conclude that Brown et al. do not describe or suggest the claimed oligomeric compounds. The examiner agrees that Brown et al. do tno teach all limitations of the claims, however this rejection is applied under 103, not 102, so all limitations are not required to be in any one reference. While Brown et al. do not teach use of nucleotide analogs as the preferred way to reduce duplex stability, they do teach this type of modification, indicating that the person of ordinary skill in the art would recognize all the techniques taught by Brown et al. would be equally likely to reduce stability, providing evidence that the use of nucleotide analogs is a matter of routine design choice.

Applicants argue that the appropriate design of chemically modified siRNA molecules having enhanced properties relative to unmodified compounds would have been unpredictable to those of ordinary skill in the art, arguing that because Fosnaugh

et al. teach away from the claimed pattern of chemical modifications, those in the art would have had no reason to select the claimed pattern of modifications from the chemical modifications taught by Fosnaugh et al. and Brown et al. Applicants further argue that oligomeric compounds with the claimed pattern of chemical modifications inhibit target RNA expression and the results taught in examples 3 and 4 of the instant application would have been completely unexpected.

Applicants' arguments regarding unpredictability of the combination of references appear to be stating that the combination of references is unpredictable because one would not know *a priori* if the claimed combination is going to have enhanced properties relative to unmodified compounds. Applicants' assertions regarding Fosnaugh et al. teaching away from the invention are addressed above. Additionally, it is noted that the claims do not recite any enhanced properties or require that the claimed compounds be superior to unmodified compounds, therefore there is no evidence of record to indicate that the choice of the claimed modifications would be more than design choice or that those in the art would expect the claimed modifications to not work, therefore there is no reason to consider the results observed in the working examples as unexpected.

Claims 1, 38, 40 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fosnaugh et al. in view of Zamore et al. (both of record).

The claims are directed to compositions of oligomeric compounds comprising a sense and antisense strand wherein the antisense strand comprises at least one 2'-fluoro nucleoside and the sense strand comprises an inosine base at the 3' terminus and a C or G at the 5' terminus. In specific embodiments the compounds are 12-30 or

19-23 nucleotides in length or the antisense comprises 2'-fluoro at each nucleotide position.

Fosnaugh et al. teach siRNAs that are about 19 to about 25 nucleotides in length and comprise an antisense region complementary to a sequence encoding a target RNA and a sense region complementary to the antisense region. At paragraph 34 Fosnaugh et al. teach the use of chemically modified siRNAs, with chemical modifications including 2'-deoxy-2'-fluoro ribonucleotides, which improve the stability of the interaction with the target RNA sequence and to improve nuclease resistance. Fosnaugh et al. additionally teach that "universal bases" may be included in a siRNA, teaching at paragraph 129 that inosine is an example of a universal base. At paragraph 50 Fosnaugh et al. teach that 2'-deoxy-2'-fluoro modified nucleotides and universal base modifications can be present in either the sense strand, the antisense strand or both strands and in Table III specifically teach 21 nucleotide siRNAs wherein the antisense strand comprises 2'-fluoro nucleosides and a G at the 5' terminus. Fosnaugh et al. teach modifications to nucleotides in a permissive manner, describing at paragraph 43 for example that a siRNA can comprise any naturally or non-naturally occurring nucleobase and also describing at paragraph 50 that a siRNA can comprise "5 or more" 2'-fluoro nucleotides, but Fosnaugh et al. does not explicitly teach a siRNA wherein every position contains a 2'-fluoro modified nucleotide, nor does this reference explicitly teach the inclusion of inosine at the 3' terminus of the sense strand.

Zamore et al. teach asymmetric siRNAs that provide enhanced specificity and efficacy for mediating RISC-mediated cleavage of a desired target gene. These siRNAs are described at paragraphs 80-82. In one preferred aspect the base pair strength

between the antisense strand 5' end and the sense strand 3' end of the siRNAs is less than the bond strength or base pair strength between the antisense strand 3' end and the sense strand 5' end, such that the antisense strand preferentially guides cleavage of a target mRNA. In one embodiment, the bond strength or base pair strength is less due to at least one base pair comprising a rare nucleotide such as inosine (I). These teachings are present in the provisional application filed June 2, 2003.

Zamore et al. demonstrate this concept in example IV, producing siRNAs having I:C base pairs at the 5' terminus of the antisense strand. When the 5' terminus of the anti-sense strand is substituted with inosine the anti-sense strand was enhanced relative to the sense strand. Thus, the strand whose 5' end is in the weaker base pair was more effective at target cleavage.

At paragraphs 89-92 Zamore et al. further teach that the siRNAs can be modified to improve stability in serum or in growth medium for cell cultures. Preferred nucleotide analogues include sugar-modified ribonucleotides where the 2'OH-group is replaced by groups such as halo, which includes fluorine.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make siRNAs comprising 2'-fluoro modified nucleosides as taught by Fosnaugh et al. with an inosine base that will produce asymmetry within the siRNA as taught by Zamore et al. Both Fosnaugh et al. and Zamore et al. suggest the use of 2'-modified nucleosides such as fluoro for the purposes of increasing nuclease resistance and Fosnaugh actually produces siRNAs where these modifications are in the antisense strand. Based on the permissive manner in which Fosnaugh et al. teach the inclusion of 2'-fluoro modified nucleotides and the knowledge that such nucleotides

can be incorporated into an oligomer using commercially available reagents and routine synthetic methods, one of ordinary skill in the art would recognize the production of a siRNA comprising 2'-fluoro nucleotides at every position of the antisense strand to be a matter of design choice that would be made in the course of routine optimization. Zamore et al. provide a motivation and reasonable expectation of success in including inosine nucleotides in a siRNA by teaching and exemplifying that inclusion of such a nucleoside reduces the base pairing strength and provides a motivation to reduce the base pair strength between the antisense 5' end and the sense 3' end by teaching that reducing strength of this particular base pair enhances cleavage of the target mRNA. While Zamore et al. exemplify the use of inosine in the antisense strand and not the sense strand, one of ordinary skill in the art would recognize that reversing the I:C base pair to place the inosine in the sense strand produces an equivalent structure that is also an asymmetric siRNA having an enhanced antisense strand.

Thus, the invention of claims 1, 38, 40 and 58 would have been obvious, as a whole, at the time the invention was made.

Response to Arguments

Applicants traverse the rejection over Fosnaugh et al. in view of Zamore et al. by arguing Fosnaugh et al. provide generalized teachings regarding chemical modification of RNA and do not provide any guidance regarding the particular types, number or positioning of chemical modifications that should be present in order to impart beneficial properties to the molecule.

This argument is not persuasive because Fosnaugh et al. explicitly contemplate an siRNA wherein the antisense strand comprises one or more 2'-fluoro modified sugars, the same limitation recited in instant claim 1 (see paragraph 52). Fosnaugh et al. also teach the presence of 2'-fluoro sugars in the antisense strand, teaching that this strand can have 5 or more such modifications, which one of ordinary skill would recognize could extend to each position of the antisense strand.

Applicants further argue that Zamore et al. describe various means for lessening the base pair strength between the 5' end of the antisense strand and the 3' end of the sense strand, but do not teach that incorporating an inosine base into an siRNA molecule is more advantageous or desirable than other means and do not suggest compositions wherein the antisense strand comprises at least one 2'-fluoro modified nucleoside.

While Zamore et al. do not teach use of inosine as the preferred way to reduce duplex stability, they do teach this type of modification, indicating that the person of ordinary skill in the art would recognize all the techniques taught by Zamore et al. would be equally likely to reduce stability, providing evidence that the use of nucleotide analogs is a matter of routine design choice. The examiner agrees that Zamore et al. do not specifically teach siRNAs with 2'-fluoro modification in the antisense strand, but they do explicitly suggest the incorporation of modified nucleotides and teach the use of halogen modifications. Those of ordinary skill recognize that fluorine is a halogen.

Applicants argue that the appropriate design of chemically modified siRNA molecules having enhanced properties relative to unmodified compounds would have been unpredictable to those of ordinary skill in the art, arguing that because Fosnaugh

et al. teach away from the claimed pattern of chemical modifications, those in the art would have had no reason to select the claimed pattern of modifications from the chemical modifications taught by Fosnaugh et al. and Zamore et al. Applicants further argue that oligomeric compounds with the claimed pattern of chemical modifications inhibit target RNA expression and the results taught in examples 3 and 4 of the instant application would have been completely unexpected.

Applicants' arguments regarding unpredictability of the combination of references appear to be stating that the combination of references is unpredictable because one would not know *a priori* if the claimed combination is going to have enhanced properties relative to unmodified compounds. Applicants' assertions regarding Fosnaugh et al. teaching away from the invention are addressed above. Additionally, it is noted that the claims do not recite any enhanced properties or require that the claimed compounds be superior to unmodified compounds, therefore there is no evidence of record to indicate that the choice of the claimed modifications would be more than design choice or that those in the art would expect the claimed modifications to not work, therefore there is no reason to consider the results observed in the working examples as unexpected.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It

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Tracy Vivlemore
Primary Examiner
Art Unit 1635

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635